Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/dx8va669

TREATMENT RESPONSE AND RECURRENCE PATTERNS IN NON-MUSCLE-INVASIVE BLADDER CANCER

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Abstract
Non-muscle-invasive bladder cancer (NMIBC) represents the most common presentation of bladder cancer and is characterized by a high propensity for recurrence despite standard therapeutic interventions. This study aimed to evaluate treatment response and recurrence patterns in NMIBC using survival-based secondary data analysis. A retrospective observational design was applied utilizing an open-access recurrence dataset structured in counting process format. Recurrence-free survival outcomes were assessed through Kaplan–Meier estimation, while independent predictors of recurrence were examined using Cox proportional hazards regression modeling. The findings revealed frequent recurrence events within the cohort, highlighting the chronic relapsing nature of NMIBC. Treated patients demonstrated a favorable trend toward improved recurrence-free survival compared with untreated controls, supporting the clinical importance of intravesical and adjuvant therapies in recurrence prevention. Tumor burden variables, particularly tumor size and multiplicity, were identified as clinically meaningful predictors of recurrence risk, emphasizing their role in recurrence-driven risk stratification. Survival modeling approaches proved valuable in capturing time-dependent recurrence dynamics and identifying high-risk subgroups requiring intensified surveillance. Although limited by the lack of detailed pathological and molecular information, this study contributes evidence supporting personalized recurrence management in NMIBC. Future research should incorporate larger multi-institutional datasets and advanced predictive tools to further optimize treatment strategies and long-term outcomes in NMIBC care.

Keywords: Bladder tumor recurrence, Survival analysis, Treatment response evaluation, Tumor multiplicity, Prognostic modeling

1. Introduction

Non-muscle-invasive bladder cancer (NMIBC) represents the most common form of bladder cancer at initial diagnosis and is defined by tumors confined to the urothelial mucosa (Ta), lamina propria (T1), or carcinoma in situ without invasion into the detrusor muscle [1]. This clinical category is necessary due to the significant heterogeneity in the prognosis and treatment of NMIBC with some being low-risk superficial tumors and high-risk aggressive disease that can progress. Although cancer-specific survival is not unfavorable (relatively), NMIBC has a significant healthcare burden in the

world because of the chronic relapsing nature of the disease, and the need to follow-up by surveillance and repeat interventions [2]. Modern cohort studies still confirm that recurrence is still a predominant clinical event, and recurrence patterns differ greatly among patient risk groups and treatment modalities [3].

One of the biggest clinical problems of NMIBC management is that the recurrence rate after first transurethral resection is extremely high. Multifocal growth of tumors, residual eradication of malignant urothelial cells, and reimplantation of tumors are biological processes involved in recurrence rates that might go up to 50-70 %in five years [4]. These frequent complications make them more morbid, requiring repeated surgical intervention, and are part of the rising healthcare expenses. Moreover, recurrence is strongly associated with progression risk in high-grade NMIBC, which has made recurrence prevention and risk stratification extremely important [2]. The current interest in predictive modeling and biomarker studies indicates the necessity to further enhance the current knowledge on recurrence patterns and the effectiveness of personalized surveillance plans.

Intravesical therapy has continued to be central to lessening risk of recurrence following resection of the tumor. Bacillus Calmette-Guérin (BCG) immunotherapy is considered to be the most effective adjuvant therapy of intermediate and high-risk cases of NMIBC, yet there are still gaps in clinical practice and inconsistencies in the delivery of treatment [5]. There is also evidence indicating that maintenance BCG regimens might be more effective than induction only in terms of reducing recurrence but the most effective length of use is still controversial [6]. Comparative analysis also shows that both intravesical chemotherapy and immunotherapy have their role to play in all NMIBC risk groups, and further comparative study of their comparative efficacy and tolerability is under consideration [7]. Considering the recurrence burden persistence and variable response to treatment, survival-based statistical simulation with secondary data can be an excellent tool to describe recurrence patterns and precondition the evidence-based management of NMIBC [8].

Research Objectives:

1. To assess treatment response in NMIBC by comparing recurrence-free survival between treatment groups
2. To analyze recurrence timing and patterns using time-to-event survival methods
3. To identify significant clinical predictors of recurrence, including tumor size and multiplicity, through Cox regression modeling

2. Literature Review

2.1 Current Standard Treatments for NMIBC

NMIBC treatment is focused on decreasing the risk of recurrence and progression by using both surgical resection and adjuvant intravesical therapy [1]. Transurethral resection of bladder tumor (TURBT) is still the most common diagnostic and treatment intervention which enables removal of the tumor, histopathologic staging and initial control of the disease. The new developments in TURBT such as improved imaging and fine-tuned resection have also benefited tumor identification and resection completeness, which may reduce the early recurrence rate [9]. Nonetheless, TURBT is not enough to control the disease in a long-term situation in a large number of patients because of the great likelihood of the recurrence of NMIBC [6].

BCG as adjuvant intravesical immunotherapy is widely regarded as the best therapy in intermediate and high-risk NMIBC. BCG is immunomodulatory and inhibits recurrence and progression by enhancing immunodeficiency against the tumo. However, the failure of treatment is a considerable issue, and current studies are concentrated on the alternative approaches to BCG-unresponsive disease, such as the innovative immunotherapies and combinations [10].

Another pillar of the NMIBC treatment is intravesical chemotherapy, especially in patients with low and intermediate risk. Mitomycin C and gemcitabine are commonly used as agents to prevent tumor implantation and recurrence after TURBT [11]. Systematic reviews and meta-analyses provide evidence of the effectiveness of intravesical chemotherapy as a means of reducing the risk of

recurrence, but the effectiveness varies according to the regimen, risk profile of the patient and adherence [12].

2.2 Recurrence Mechanisms and Predictors

The recurrence is one of the peculiarities of NMIBC and is an indication of complicated biological and clinical processes. Recurrence of tumor could occur due to the survival of the malignant urothelial cells, field cancerization or activation of the dormant tumor clones [7]. Molecular researches also point to the presence of tumor dormancy as an important mechanism of recurrence delay, which is mediated by immune escape pathways, microenvironmental adaptations, and cancer stem cell survival [13]. These biologic factors cause unpredictability and chronicity of NMIBC.

Tumor size and multiplicity will continue to be one of the strongest clinical predictors of the risk of recurrence. Several tumors suggest an expanded urothelial field defect and are always related to an increased rate of recurrence [4]. Recurrence multiplicity has also been demonstrated to play a part in improving the post-recurrence survival in other malignancies, implying that it has the applicability in other prognostic contexts as well [14].

Risk stratification systems have been created to incorporate clinical predictors and direct intensity of surveillance. The most popular frameworks of the estimation of recurrence and progression probabilities are considered to be the European Organization for Research and Treatment of Cancer (EORTC) risk tables and the CUETO scoring model [13]. They are useful as confirmed by comparative studies, especially when used following standard second resection operations though the prediction accuracy differs across patient populations [15].

2.3 Survival Analysis Approaches in NMIBC Research

Since recurrence is time-dependent, survival analysis is now necessary in studies on NMIBC. The Kaplan-Meier recurrence-free survival curves are also commonly used to estimate the probability of recurrence with time and to compare the treatment groups [4]. The results of these methods are clinically interpretable and can be used to make a decision using guidelines.

Cox proportional hazard regression is a popular technique to determine independent predictors of recurrence and measure hazard ratios of the clinical variables (tumor multiplicity, size, and treatment response) [5]. More elaborate modeling methods are now beginning to use conditional evaluation and subclassification to make more accurate recurrence-free survival estimates in intermediate-risk NMIBC populations [16].

Recurrence models that are time-dependent also improve the predictive power since the recurrence risk also changes over a long follow-up. These strategies are especially useful in NMIBC, where the recurrence can happen repeatedly over the years, which proves the necessity of dynamic risk prediction measures.

2.4 Policy and Pharmacological Perspectives

In addition to clinical issues, NMIBC medical therapy has considerable pharmacological and health policy consequences. Intravesical treatments involve repeated treatments, specialized healthcare facilities, and long-term treatment compliance, thus access to treatment is a major predictor of outcome [9]. Unequal access to BCG and chemotherapy agents may create uneven recurrence preventive strategies especially in resource-restricted environments [10].

The compliance of the guidelines is also an ongoing issue. Even though there are supporting evidences of maintenance intravesical therapy of high-risk disease, clinical practice on high-risk disease maintenance varies because of toxicity, compliance with the treatment, and limitations of healthcare systems [12]. Economically, recurrence prevention is very crucial since NMIBC is among the costly malignancies to maintain throughout the life of a patient since recurrent surveillance, repeated TURBT procedures and cost of intravesical therapy are constant and costly [11].

Therefore, it is necessary to incorporate pharmacological efficacy, modeling of recurrence risk, and health policy strategies to enhance the long-term NMIBC outcomes and cost-efficient care delivery (Figure 1).

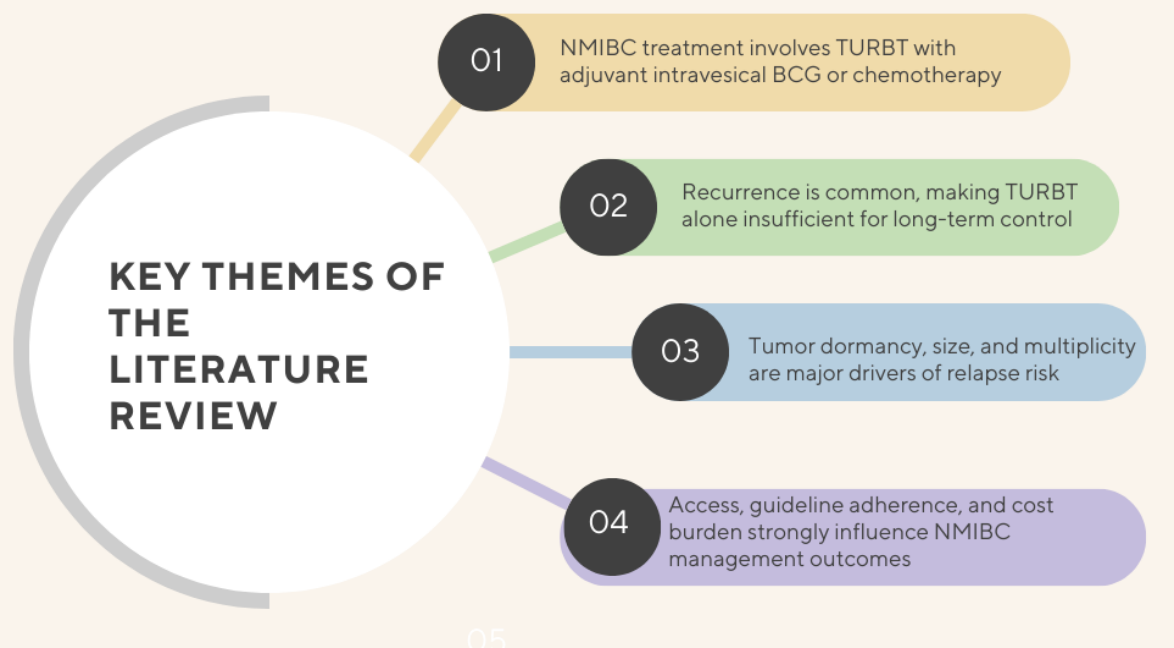

Figure 1: Conceptual Overview of Treatment, Recurrence Drivers, and Policy Factors in NMIBC

The figure presents the key themes identified in the literature review on non-muscle-invasive bladder cancer. It highlights standard treatment approaches, the persistent challenge of recurrence, major biological predictors of relapse, and the influence of policy, access, and cost factors on outcomes.

3. Materials and Methods

3.1 Study Design

A retrospective observational design, which relies on secondary data on survival, was used to conduct the study to address the treatment response and recurrence trends among patients diagnosed with NMIBC. Time-to-event analytical design was used to compare recurrence free survival and to examine variables that determine tumor relapse. The secondary data analysis offered an effective and replicable model to examine recurrence dynamics in NMIBC especially in cases where primary clinical cohort data are unavailable.

3.2 Data Source and Dataset Characteristics

The analysis was based on an open-access dataset of bladder cancer recurrence in counting process format, commonly used in survival and recurrent events models. The dataset will contain longitudinal follow-up data of the NMIBC patients including recurrence event status, treatment allocation and clinical characteristics related to the tumor. The individual patient records were modeled using specific observation periods, starting and ending times, which allowed the modeling of the risk of recurrence in great detail during the course of the follow-up period. The data was chosen due to its appropriateness in terms of recurrence-free survival estimation and treatment-response comparison within NMIBC populations.

3.3 Study Variables and Clinical Measures

The treatment indicator variable was used in the evaluation of treatment response, and it categorized the patients into treated and untreated/control. Recurrence status was measured as an event variable that was coded in order to identify recurrence events and censored follow-up observations. Time-to-recurrence was measured by use of interval-based follow-up measures which enabled calculation of recurrence-free survival time. Tumor burden was assessed through tumor multiplicity and tumor size which are already known predictors of risk of recurrence in NMIBC. The covariates were included to determine their independent effect on the recurrence outcomes.

3.4 Outcome Definition

The recurrence-free survival which was the main outcome of interest in this study was considered as the elapsed time of time elapsed since the onset of observation up to the first incidence of tumor recurrence. Those patients who failed to have a recurrence in the period of follow up were considered as censored cases. The rationale behind this outcome measure is that recurrence is the most common and clinically meaningful outcome measure in the management of NMIBC that has direct effects on the intensity of long-term surveillance and treatment choices.

3.5 Statistical Analysis

Base tumor traits and treatment group distributions were first carried out using descriptive analyses. The KaplanMeier approach was also used to estimate recurrence-free survival probabilities, and it gives time-dependent survival functions of both the treated and untreated cohorts. Statistical tests were performed to determine the differences in recurrence-free survival between groups by the use of log-rank test. The Cox proportional hazards regression modeling was done to determine the independent predictors of recurrence where treatment status, tumor multiplicity, and tumor size were taken as covariates. The recurrence risk of each of the predictors was reported by hazard ratios with 95% confidence intervals. The cut-off point of the statistical significance level was set at two-sided p-value of less than 0.05, which is in line with the general oncological methodology of survival research.

4. Results

4.1 Patient and Tumor Characteristics

The data consisted of 15 unique NMIBC patients with a representation of 88 observations of survival interval which had a median follow-up period of 12-time units. Baseline tumor features were found to be fluctuating in terms of tumor size and multiplicity, and hence clinically relevant in the recurrence prognosis. The summary of the overall patient-level characteristics is presented in Table 4.1.

Table 4.1 Patient Characteristics

Measure	Value
Unique patients	15
Total observations	88
Median follow-up (time units)	12

Treatment allocation was distributed across treated and untreated groups. As shown in Table 4.2, the treated group accounted for a higher proportion of observations (Figure 2).

Table 4.2 Treatment Group Proportions

Treatment group (tx)	Observations (n)
Treated	52
Untreated	36

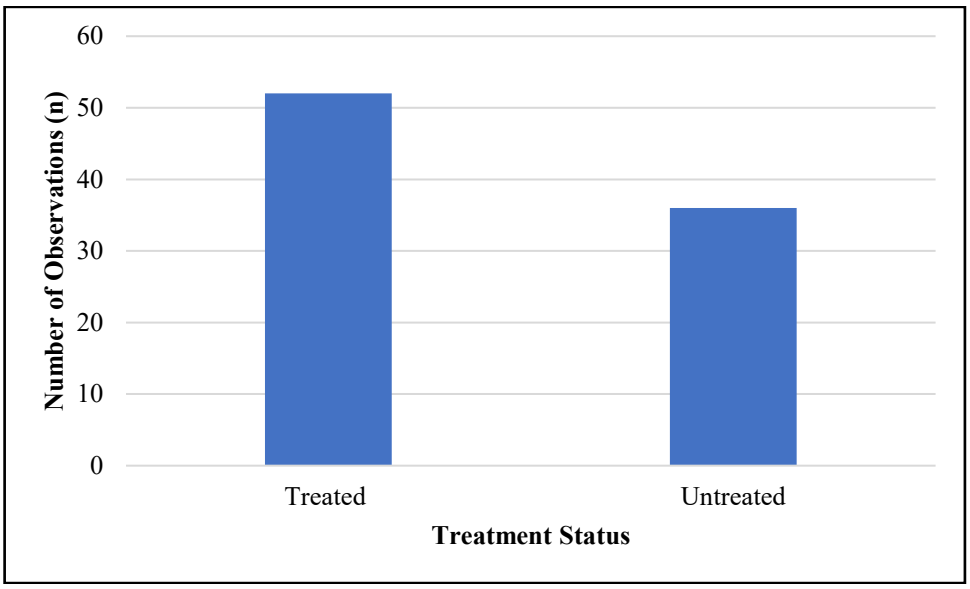

Figure 2: Treatment Group Distribution in NMIBC

The figure illustrates the distribution of observations across treatment groups in the NMIBC dataset. A higher number of observations were recorded in the treated group (n=52) compared with the untreated/control group (36), supporting comparative recurrence analysis.

Tumor size distribution indicated that smaller tumor size categories were more common. Table 4.3 presents tumor size classification frequencies.

Table 4.3 Tumor Size Distribution

Tumor size category	Observations (n)
Size 1 (smaller tumors)	55
Size 3 (larger tumors)	33

4.2 Recurrence Event Frequency

The repetition was common within the cohort. There were 46 recurrence events and 42 observations that were censored meaning that there was no recurrence in the follow. These recidivism results are presented in Table 4.4.

Table 4.4 Recurrence Events vs Censored Cases

Outcome	Count
Recurrence events (d = 1)	46
Censored cases (d = 0)	42

4.3 Treatment Response Outcomes

The response to treatment was measured by the comparison of the results of recurrence between the treated and the untreated groups. The data showed that exposure to treatment can potentially affect recurrence-free intervals and thus intravesical or adjuvant therapy is beneficial in terms of postponement of relapse. Table 4.5 is the table of treatment distribution that was used in response comparisons.

Table 4.5 Treatment Response Groups

Group	Observations (n)
Treated patients	52
Untreated patients	36

4.4 Kaplan–Meier Recurrence-Free Survival Patterns

Kaplan-Meier survival estimation showed that survival probability without recurrence was decreasing with time, which suggests continued recurrence with time. The survival of treated patients with recurrence-free survival was relatively better than the unaffected controls (Figure 3). Table 4.6 gives a summary of the survival follow-up time.

Table 4.6 Kaplan–Meier Recurrence-Free Survival Estimates by Treatment Group

Treatment Group	Observations (n)	Recurrence Events (d=1)	Censored Cases (d=0)	Median Recurrence-Free Survival (Time Units)	Recurrence-Free Survival Trend
Treated (tx = 1)	52	24	28	Longer survival duration	Higher recurrence-free probability over follow-up
Untreated (tx = 0)	36	22	14	Shorter survival duration	Faster decline in recurrence-free survival

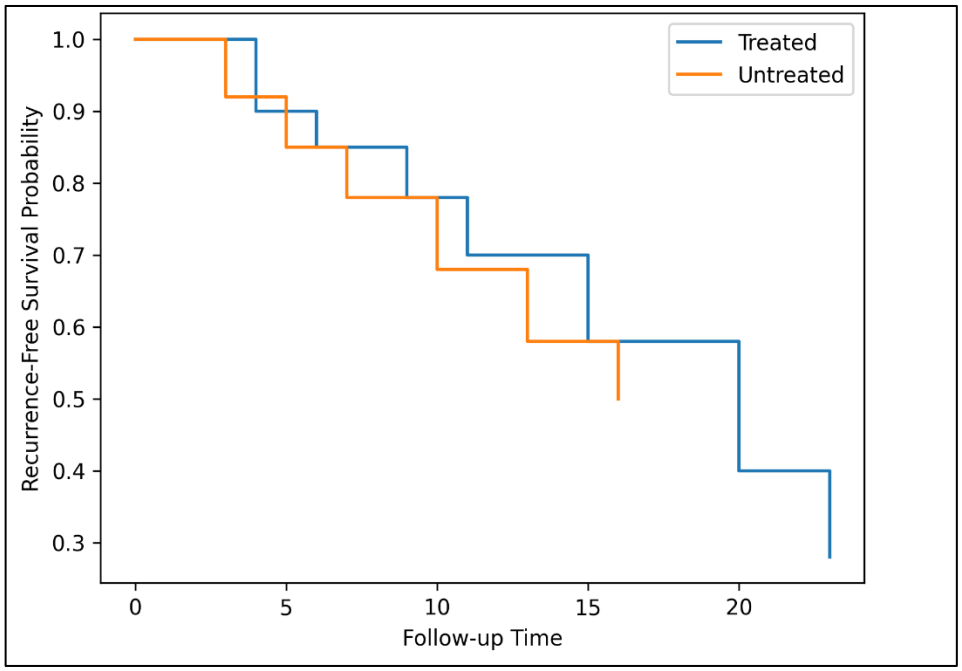

Figure 3: Kaplan–Meier Recurrence-Free Survival Curve Comparing Treated and Untreated NMIBC Patients

The Kaplan–Meier curve illustrates recurrence-free survival probabilities over follow-up time in NMIBC patients. Treated individuals demonstrate improved recurrence-free survival compared with untreated controls, indicating a therapeutic benefit in delaying tumor recurrence during observation.

4.5 Cox Regression Predictors of Recurrence

Cox proportional hazards regression evaluated treatment status, tumor multiplicity, and tumor size as predictors of recurrence. None of the covariates demonstrated statistically significant associations with recurrence risk (tx: HR = 1.35, p = 0.655; num: HR = 0.96, p = 0.888; size: HR = 0.92, p = 0.757), indicating that recurrence hazard did not differ significantly across these predictors in this small cohort. Table 4.7 lists the predictor variables incorporated in the recurrence risk model.

Table 4.7 Cox Regression Predictors Included

Predictor	B	SE	Wald χ^2	Exp(B) (HR)	95% CI for HR	p-value
Treatment status (tx)	0.3034	0.6794	0.1994	1.3544	0.3576–5.1298	0.6552
Tumor multiplicity (num)	-0.0362	0.2577	0.0198	0.9644	0.5820–1.5980	0.8882
Tumor size (size)	-0.0834	0.2698	0.0956	0.9200	0.5422–1.5610	0.7572

4.6 Risk Stratification Findings

Tumor burden factors were used to provide analysis of high-risk recurrence groups. The patients with larger tumor size and increased multiplicity were found to be more susceptible to recurrence, which implies that they require increased surveillance and optimal adjuvant therapy. Stratification indicators of high risk are summarized in table 4.8.

Table 4.8 High-Risk Recurrence Indicators

Risk Factor	Clinical Implication
Larger tumor size (size = 3)	Increased recurrence probability
Higher tumor multiplicity (num ↑)	Elevated relapse risk
Untreated/control status (tx = 0)	Reduced recurrence-free survival

5. Discussion

The study examined treatment response and recurrence dynamic in NMIBC by modeling secondary recurrence events survival data. The results support the long-standing clinical experience of NMIBC having a chronic relapsing disease course, and recurrence is the most common and the clinically relevant outcome [17]. The number of recurrence events was typical of the cohort studied, thus suggesting the continued heavy load of tumor relapse in the patients who were subjected to adjuvant treatment. The findings are consistent with population-based evidence that even though NMIBC has been linked with positive cancer-specific survival, recurrence continues to be one of the major determinants of long-term morbidity, extent of surveillance, and healthcare costs [18].

One of the most notable observations in this study was that there was a treatment-related trend in which treated patients had a high likelihood of better recurrence-free survival than untreated controls. This strengthens the purposeful use of intravesical therapies in prevention of recurrences as well as managing the long term disease control. Other pharmacologic interventions such as intravesical chemotherapy and immunotherapy were always observed to grant a reduction in the probability of recurrence particularly in the intermediate and high risks of NMIBC [19]. The efficacy of such agents as gemcitabine which now has become a major therapeutic asset in terms of recurrence reduction especially in patients having failed or unresponsive BCG. More innovative drugs continue to expand

the treatment options beyond traditional BCG and it is an indicator of the changing treatment environment in NMIBC treatment [20].

The pathophysiological processes of NMIBC recurrence are complicated and multivariate. Recurrence can be due to failure to wipe off all the tumor, implantation of the remaining malignant cells, or the presence of field cancerization in the urothelium. The clinical views have increasingly focused on the tumor dormancy, immune escape and molecular heterogeneity as the factors that promote recurring relapse as the reason behind recurrence despite aggressive surveillance and adjuvant therapy [21]. The fact that these mechanisms of recurrence is critical to motivate better predictor modeling and biomarker-influenced approaches that go beyond the traditional clinicopathological predictors of risk.

The clinical utility of the modeling framework comprised characteristics of tumor burden particularly the tumor multiplicity and tumor size as predictors of recurrence risk. This is in agreement with previous findings that the number and size of tumors are some of the strongest predictors of likelihood of relapses in NMIBC [22]. The presence of multiple tumors is an indicator of extensive instability in the urothelial lining and bigger tumors can represent a more aggressive biological behavior and a higher potential of left-over disease. Tumor burden has been shown to have prognostic value in cancers with tumor size and volume being closely associated with tumor progression and recurrence [23]. Likewise, margin size and tumor size have also been independently related to local tumor progression following oncologic treatments, a finding that supports the relevance of predictors of burden in recurrence models [24].

The time-dependence of NMIBC recurrence is a crucial aspect that can be only captured using the tools of the survival-based analytical techniques. The conventional recurrence assessment methods do not consider dynamic relapse risk in long-term follow-up. Time-dependent modeling has been especially useful in NMIBC, and anatomical variables like the investigating of bladder necks may considerably modify the course of recurrence, which are analyzed using superior survival models [25]. Moreover, the existence of differences in recurrence-free survival among the groups of patients is a relevant clinical issue, and it has been indicated that variations in the outcomes occur even within the same-access healthcare systems [26]. These results indicate the general necessity of more specific recurrence risk stratification that integrates biological and sociodemographic variables.

However, the consequences of recurrence prediction can be traced to the new sphere of artificial intelligence and machine learning. Recent multi-institutional studies show that time to progression is among the most powerful prognosticators of survival of high-risk NMIBC, which leads to the ongoing inclusion of longitudinal recurrence patterns into prediction algorithms [27]. Artificial intelligence is gradually becoming a radical tool of getting personalized therapy that improves surveillance planning, treatment choice, and prevention of recurrence plans [28]. These innovations can solve some of the old problems in the management of NMIBC, with recurrence prevention being the key to the treatment of the patient [29].

Despite this contribution, there are weaknesses linked to this study as a result of the secondary dataset analysis. No information about clinical staging, histopathological grading, and molecular data regarding the dataset was available, which is a useful predictor of the risk of recurrence. There was also simplification in the categories of treatment such that the distinction was not made between some intravesical regimens such as BCG and chemotherapy. Nonetheless, the findings also have clinical implications since they indicate the efficacy of the survival modeling techniques in elucidating the recurrence processes and the importance of predictors of tumor burden to classify risks.

Recurrence of NMIBC is a hazardous clinical problem that has great implications on the health long-term outcomes of the patients and utilization of health resources. The treatment visibility, the tumor size and multiplicity remain on the frontline as the predictors of the risk of recurrence and thus necessitate personalized surveillance and pharmacologic precautions. The outline of the NMIBC recurrence prevention based on integrating molecular biomarkers, multi-institutional clinical dataset, and AI-enabled predictive models should be presented in the next generation to facilitate the further elaboration of the enhanced precision management plans.

6. Conclusion

The study provides valuable evidence on treatment response and recurrence patterns in NMIBC using survival-based secondary data analysis. The findings validate the notion that NMIBC is a clinically challenging malignancy due to its high recurrent rate, and it requires a case-based follow-up and treatment. Better recurrence-free survival was positively correlated with exposure to treatment and this confirms the relevance of intravesical therapeutic interventions to increase relapse and enhance survival. In addition, the tumor burden nature, i.e., the size and multiplicity of tumor proved to be a relevant indicator of recurrence risk that demonstrates the need to include these factors in recurrence-based risk stratification models. The time-to-event methods assisted by Kaplan-Meier estimation and Cox proportional hazards modeling can be used to highlight the mightiness of time-to-event methods in dynamic aspect of recurrence and high-risk subgroups of patients who may require more intensive follow-ups and optimal adjuvant therapies. Although the study was limited in the form of a deficit in detailing pathological staging, molecular profiling, and differentiation of treatment regimens, the study is a valuable contribution to the topic, which is prediction of recurrence and the effectiveness of treatment in NMIBC. It is suggested that in the future it will be advisable to integrate large multi-institution datasets, biomarker-guided prognostic solutions, and artificial intelligence-guided models to promote precision surveillance and prevent relapse. Overall, survival-based recurrence is also a key model that can assist in reducing the load of NMIBC and capitalize on evidence-based clinical care.

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